Meta-analysis of rare events in drug safety studies: A unifying framework for exact inferences

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Outline

For meta-analysis of rare events, I will present

Part I An exact approach by combining *p*-value functions

Part II A unifying framework for exact inferences

Part I An exact approach by combining *p*-value functions

- Liu, Liu and Xie, 2014, *JASA*, 109, 1450-1465.

A Motivating Example

Nissen and Wolski (2007, *N. Engl. J. Med.*)

- Performed a meta-analysis of 48 independent clinical trials.
- Examine if the diabetes drug *Avandia* is associated with some **adverse events** (e.g. myocardial infarction).

Study ID	Treatment		Control	
	x_i	n_i	y_i	m_i
1	2	357	0	176
2	2	391	1	207
3	1	774	1	185
⋮	⋮	⋮	⋮	⋮
46	0	25	0	24
47	0	196	0	195
48	0	676	0	225

Result and impact of Nissen and Wolski's meta-analysis

Result: common odds ratio (OR) (Peto's method)

- 95% confidence interval=(1.03 1.98);
- *P*-value=0.03 for testing $H_0 : \text{OR} = 1$ *vs* $H_1 : \text{OR} \neq 1$.

Conclusion: *Avandia* is significantly associated with myocardial infarction.

"Significant" impacts:

- The stock price of GlaxoSmithKline (GSK) dropped 7.8% on a single day.
- An alert issued by FDA immediately.
- Over 1000 lawsuits against GSK.
- US sales in 2Q 2007 dropped 22% compared to 2006.

Controversy 1: zero total event studies

A **zero total event study** refers to a study that does not observe any event in both treatment and control arms.

Avandia data: 10 zero total event studies out of 48 studies.

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Controversy 1: zero total event studies

Popular meta-analysis methods:

- Standard inverse-variance method
- Mantel-Haenszel (MH) method
- Peto's method (used by Nissen and Wolski, 2007)

How do these methods handle zero total event studies?

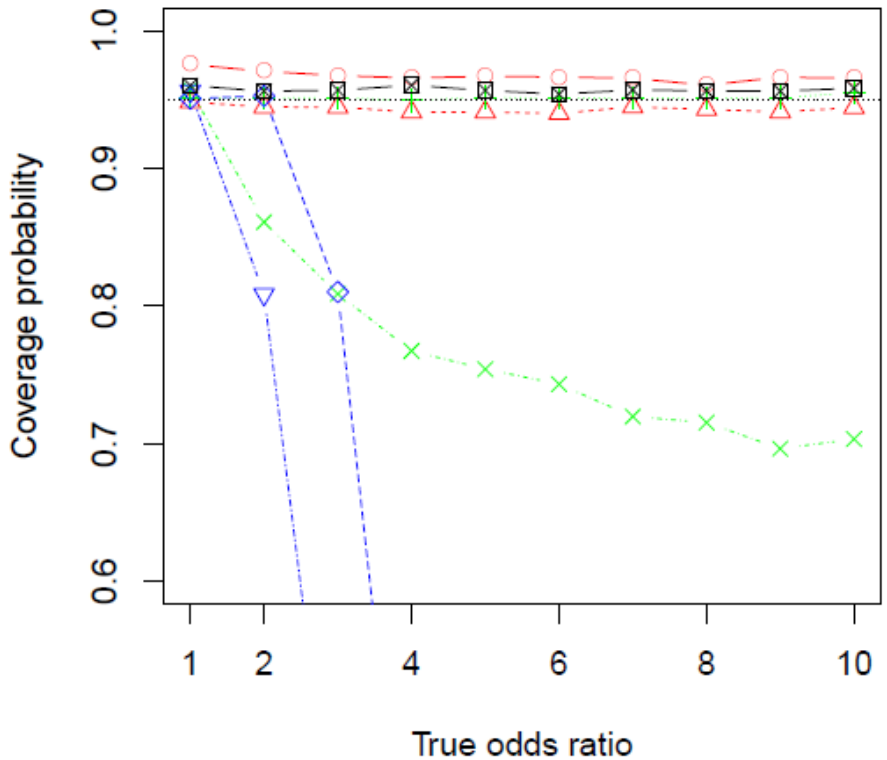
- Exclude from analysis (Nissen and Wolski, 2007);
- Add 0.5 to zero cells.

Both have undesirable impact on inference.

Question 1: Can we use all available data without artificially assigning numbers to zero events?

Controversy 2: asymptotics for rare events?

Empirical coverage probability of 95% confidence interval
– based on simulated data similar to Avandia data



Question 2: Can we develop a general exact meta-analysis framework for discrete data?

Nissen and Wolski's study raised

Question 1: Can we use all available data without artificially assigning numbers to zero events?

Question 2: Can we develop a general exact meta-analysis framework for discrete data?

Our answer: Yes!

Problem setting

Consider K independent trials with treatment and control.

- $X_i \sim Binom(n_i, \pi_{1i})$ and $Y_i \sim Binom(m_i, \pi_{0i})$.
- The odds ratio

$$\psi = \frac{\pi_{1i}/(1-\pi_{1i})}{\pi_{0i}/(1-\pi_{0i})} \quad (i = 1, \ldots, K)$$

  is often assumed being constant across the studies.
- Question: how to infer ψ when π_{1i} and π_{0i} are **extremely low**.

$$\hat{\psi}_i = \frac{x_i/(n_i - x_i)}{y_i/(m_i - y_i)} \quad (i = 1, \ldots, K)$$

Note: our following discussion applies to inference for a general parameter ψ in discrete data.

Meta-analysis principles

- Conventional principle – combining point estimates

$$\hat{\psi}_c = \frac{1}{\sum_{i=1}^{K} w_i}(w_1\hat{\psi}_1 + \cdots + w_K\hat{\psi}_K)$$

- Our new approach– combining *p*-value functions

$$p_c(\psi) = \Phi\left(\frac{1}{\sqrt{\sum_{i=1}^{K} w_i^2}}\left(w_1\Phi^{-1}(p_1(\psi)) + \cdots + w_K\Phi^{-1}(p_K(\psi))\right)\right)$$

  - What is a *p*-value function?
  - Why do we use such a combining formula?

What is a *p*-value function?

To make inference for ψ, we consider testing the hypothesis

$$H_0 : \psi = \psi^* \text{ versus } H_1 : \psi > \psi^*,$$

where ψ^* is an arbitrary but fixed value on the parameter space.

We suppose that

- a *p*-value $p_i(\psi^*; X_i, Y_i)$ can be obtained based on an **exact** test from the i-th study.

Example: Using the mid-p adaption of Fisher's exact test, we obtain a p-value for the odds ratio:

$$p_i(\psi^*; x_i, y_i) = \text{pr}_{\psi^*}(X_i > x_i \mid T_i = t_i) + \frac{1}{2}\text{pr}_{\psi^*}(X_i = x_i \mid T_i = t_i).$$

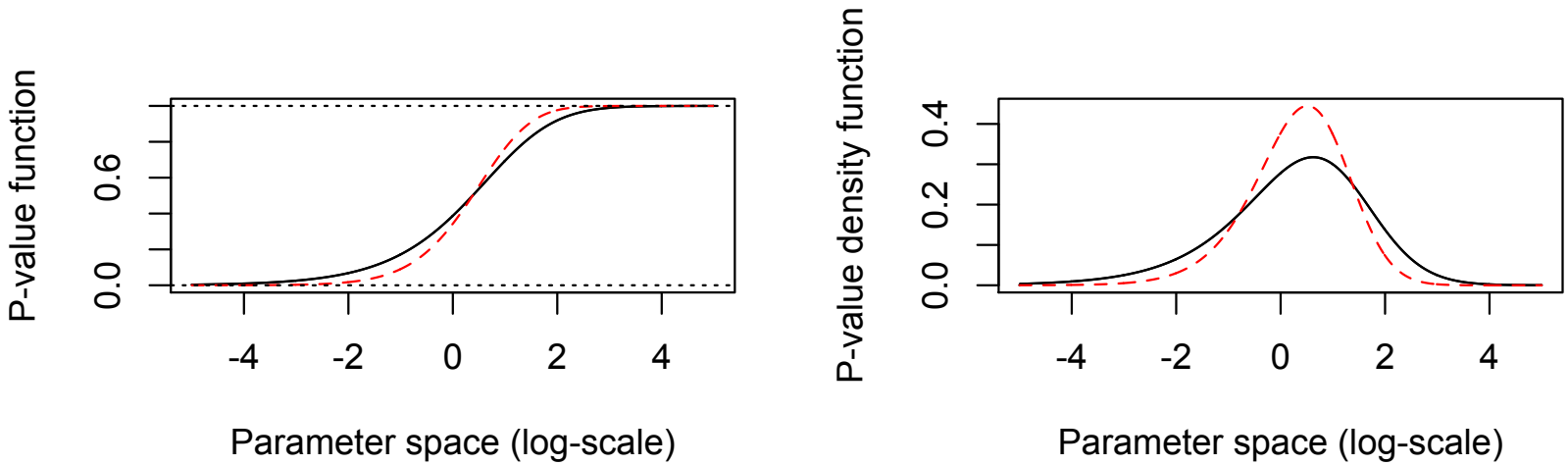
where X_i follows the noncentral hypergeometric distribution conditional on $T_i = X_i + Y_i = t_i$

Remarks on the p-value function

- The p-value $p_i(\psi^*; X_i, Y_i)$ is a function defined on both the parameter space and sample space.
- Given the sample (x_i, y_i), the function $p_i(\cdot; x_i, y_i)$ is typically a **distribution function on the parameter space**.
- This distribution function $p_i(\cdot)$ is called a **p-value function** or a **significance function** (Fraser, 1991, *JASA*).
- The p-value function $p_i(\cdot)$ can be viewed as a "distribution estimate" of the unknown parameter.

  • Schweder and Hjort, 2002, *Scand. J. Statist.* • Singh et al., 2005, *Ann. Statist.* • Xie et al., 2011, *JASA* • Fraser, 2011, *Statist. Sci.* • Xie and Singh, 2013, *Int. Statist. Rev.* •

P-value function curves



Black solid curve – an individual *p*-value function

• Obtained by using the mid-*p* adaptation of Fisher exact test on odds ratio in a study that observes $x_i = 1$ and $y_i = 3$ with sample sizes $(n_i, m_i) = (15, 60)$.

Red dashed curve – the combined *p*-value function

• Obtained by combining two independent copies of the above individual *p*-value function.

How to combine *p*-value functions?

$$p_c(\psi) = \Phi\left(\frac{1}{\sqrt{\sum_{i=1}^{K} w_i^2}}\left(w_1\Phi^{-1}(p_1(\psi)) + \cdots + w_K\Phi^{-1}(p_K(\psi))\right)\right)$$

- $p_1(\psi), \cdots, p_K(\psi)$ are *p*-value functions.
- $\Phi(\cdot)$ is the CDF of the standard normal distribution.
- w_i is the weight assigned to the i-th study.

The simple combining formula yields statements that explicitly account for the impact of individual studies on the overall inference (e.g., efficiency/power, type I error rate).

Inference from a *p*-value function

The combined *p*-value function $p_c(\psi)$ can be used for making inference for the parameter ψ.

- **Point estimate**. The median of the distribution $p_c(\psi)$, namely $\hat{\psi}_c = p_c^{-1}(1/2)$, can be used as a point estimator.
- **Interval estimate**. The interval $(p_c^{-1}(\alpha/2), p_c^{-1}(1-\alpha/2))$ can be used as a $100(1-\alpha)\%$ confidence interval.
- ***P*-value**. The value of $p_c(\psi^*)$ can be readily used as the overall *p*-value for testing the hypothesis $H_0 : \psi = \psi^*$ vs $H_1 : \psi > \psi^*$.

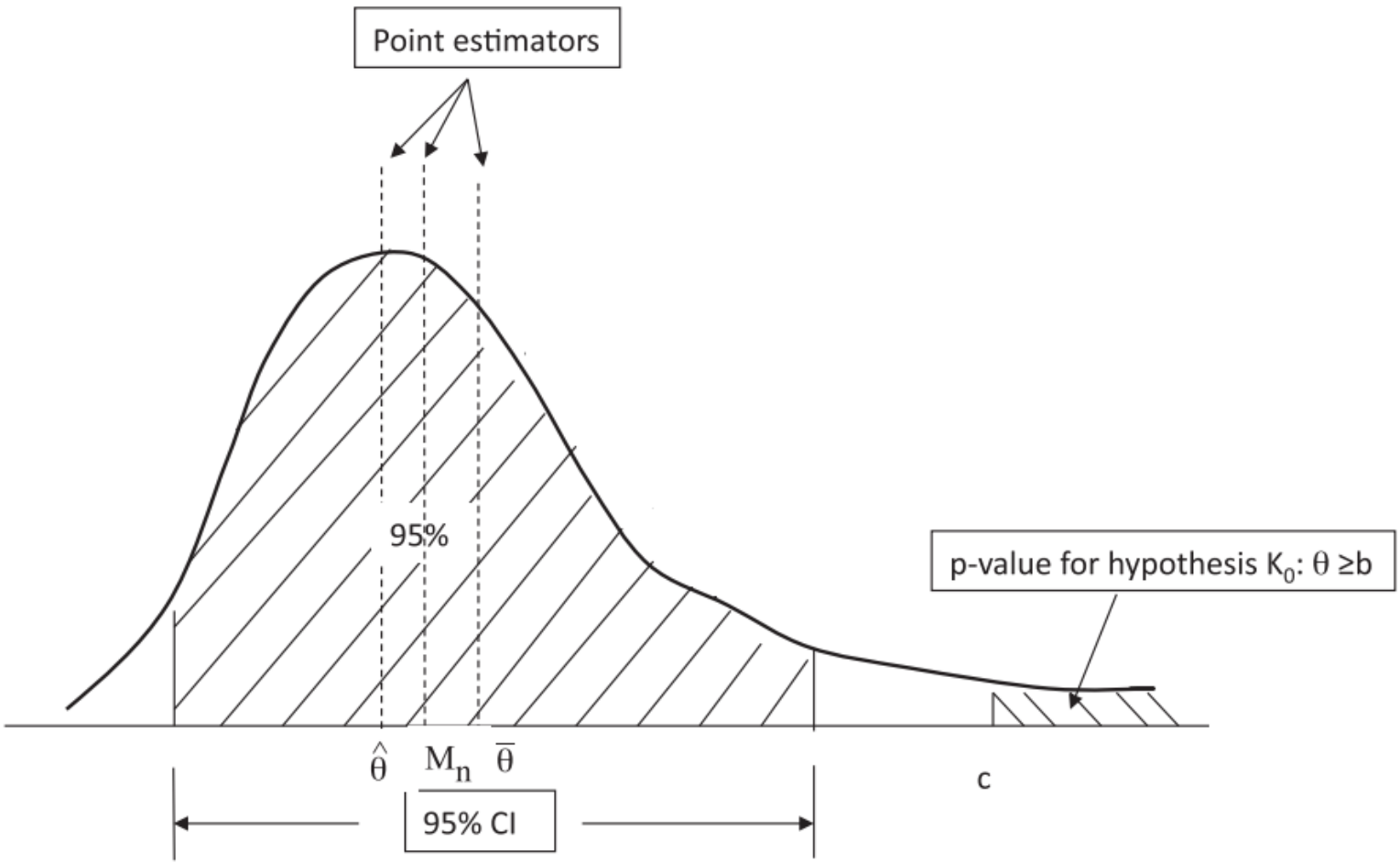


Figure 1. *The plot is a graphical illustration on making inference using a confidence distribution, including examples of point estimators (mode $\hat{\theta}$, median M_n and mean $\bar{\theta}$), a level 95% confidence interval and a one-sided p-value.*

Preview of desirable properties

- Practical usefulness
  – Our approach includes in the analysis all available data, including zero total event studies, without using any artificial correction for zero event.
- Methodological broadness
  – Our framework encompasses a broad class of exact meta-analysis methods, as it permits broad choices for the combining elements, such as tests used in individual studies, and any parameter of interest.
- Theoretical soundness
  –Our approach yields statements that explicitly account for the impact of individual studies on the overall inference (efficiency/power and type I error rate).
- Numerical superiority
  –Our approach outperforms existing commonly used meta-analysis methods in the setting of rare events.

Data sets used in numerical studies

1. Avandia data (Nissen and Wolski, 2007, Table 3).
   - K=48;
   - median(n_i)=222, median(m_i)=142.
   - 10 zero total event studies.

2. Promotion data (Gastwirth, 1984, Table 8).
   - K=10;
   - median(n_i)=25, median(m_i)=9.
   - Zero events in one arm across all studies.

Promotion data

Study ID	Whites		Blacks	
	x_i	n_i	y_i	m_i
1	4	20	0	7
2	4	17	0	7
3	2	15	0	8
4	1	18	0	8
5	1	18	0	8
6	1	30	0	10
7	2	31	0	10
8	1	31	0	10
9	1	30	0	10
10	1	34	0	13

Simulation setting

We mimic the data structure of Avandia data or promotion data.

- $K = 48$ 2×2 tables with the row margins being the same as the tables in Avandia data (or promotion data, $K = 10$).
- A fixed odds ratio (OR) ranging from 1 to 10.
- $\{\pi_{0i}, i = 1, 2, \ldots, 48\}$ are generated from U(0, ξ), where $\xi = 0.01, 0.05, 0.1$.
- $\{\pi_{1i}, i = 1, 2, \ldots, 48\}$ are determined by

$$logit(\pi_{1i}) = log(OR) + logit(\pi_{0i})$$

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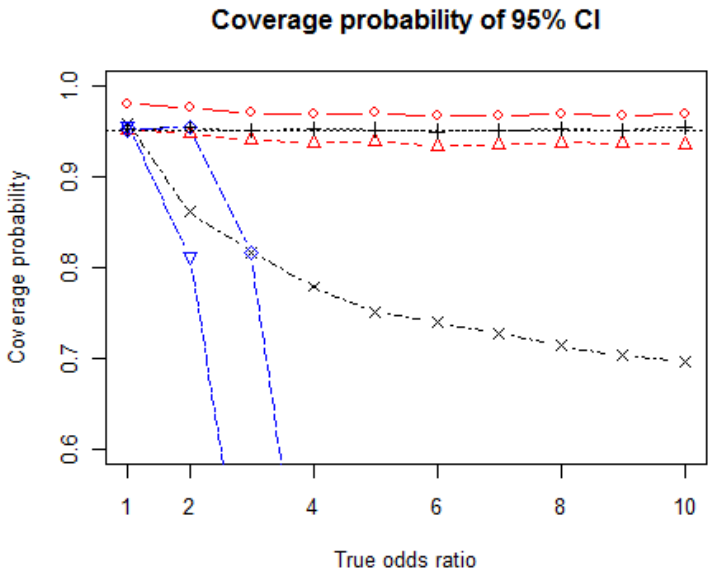
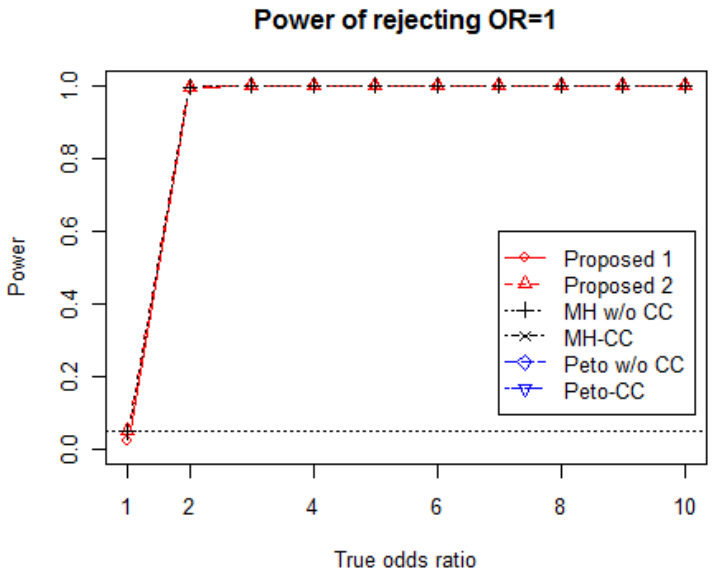
Methods for numerical comparison

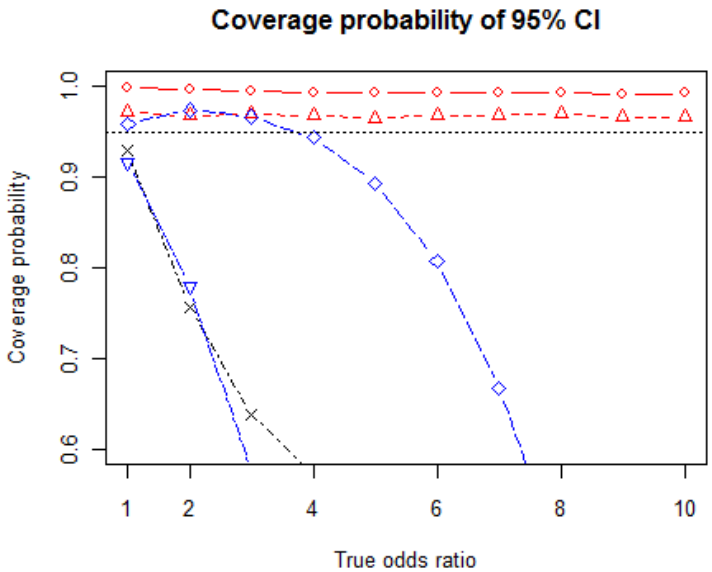
- Combining the *p*-value functions;
- Combining the beta-adjusted *p*-value functions;

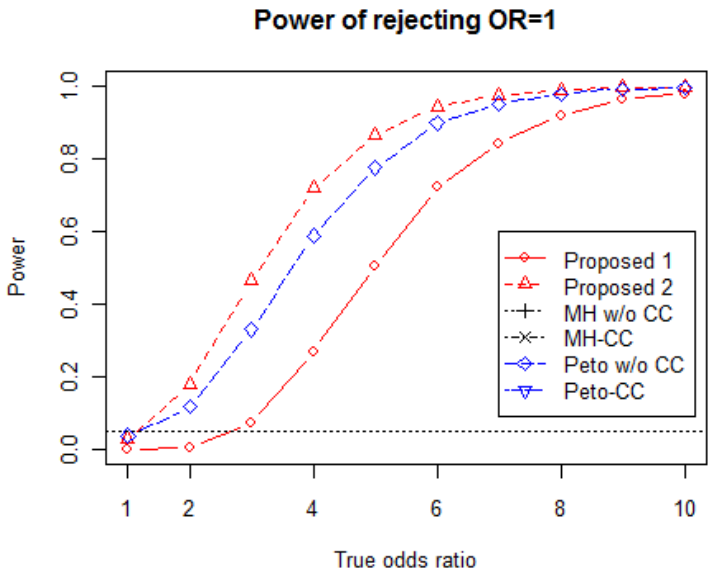
- MH method without CCs (excluding zero total event studies);
- MH method with 0.5 CCs for zero events;

- Peto's method without CCs (excluding zero total event studies);
- Peto's method with 0.5 CCs for zero events.


Coverage probability of 95% CI
Coverage probability
True odds ratio


Power of rejecting OR=1
Power
True odds ratio
Proposed 1
Proposed 2
MH w/o CC
MH-CC
Peto w/o CC
Peto-CC


Coverage probability of 95% CI
Coverage probability
True odds ratio


Power of rejecting OR=1
Power
True odds ratio
Proposed 1
Proposed 2
MH w/o CC
MH-CC
Peto w/o CC
Peto-CC

Real data analysis

	Avandia data		Promotion data	
	95% CI	*P*	95% CI	*P*
Proposed exact	(0.972, 2.001)	0.071	(0.842, ∞)	0.080
Proposed exact (adj)	(1.037, 2.004)	0.029	(1.054, ∞)	0.042
MH	(1.029, 1.978)	0.033	-	-
MH-CC	(0.919, 1.647)	0.163	(0.738, 5.396)	0.174
Peto	(1.031, 1.979)	0.032	(1.522, 12.86)	0.006
Peto-CC	(0.921, 1.659)	0.158	(0.776, 4.270)	0.168

CI: confidence interval;
P: *p*-value for hypothesis testing $H_0 : \psi = 1$ versus $H_1 : \psi \neq 1$;
adj: apply beta adjustment to individual *p*-value functions;
CC: add 0.5 continuity corrections to zero events.

Summary

Meta-analysis for discrete data

$\Downarrow$

Combining point estimates

$\Downarrow$

Combining *p*-value functions based on exact tests

Part II A unifying framework for exact inferences

- LLX's method of combining *p*-value functions
- Tian et al.'s method of combining confidence intervals – (Tian et al., 2009, Biostatistics)